106. (New) The method of claim 90 ~~or~~ 99, wherein said spinal cord injury results from a chemical trauma.

REMARKS

Upon entry of these amendments, claims 88, 90, 91, 97, 99, 105, and 106 are pending. Applicants have canceled claims 82, 84, 93-94, 96, 100, and 102-104 without prejudice to later prosecution in this or another application. Applicants have amended claims 88 and 90 to introduce subheadings. The subheadings make clearer that the stimulation of N-CAM or L1 isoform production by an NG108-15 cell *in vitro* is a functional limitation on the morphogen, not a step in the claimed methods. Applicants have also amended claims 88, 90, 97, and 99 to recite that administration of morphogen restores motor function, as recited in the preambles. Applicants have amended claims 88, 90, 97, and 99 to replace the term "skeleton" with the term --domain--. Support for this amendment is found in the specification, pg. 33, lines 31-33; and pg. 39, lines 20-27. Applicants have amended claims 88 and 90 to recite --amino acid homology--. Support for the term "amino acid homology" is found in the specification, pg. 39, line 34.

Applicants have amended claims 88 and 90 to recite a morphogen amino acid sequence encoded by a nucleic acid that hybridizes to the nucleic acid encoding the C-terminal seven-cysteine domain of human OP-1. Support for the hybridization definition is found in the specification at pp. 64-67, Example 1. Specifically, the specification teaches that appropriate probes for morphogen detection include any probe capable of hybridizing specifically to a transcript, and distinguishing the transcript from other related transcripts (*see*, specification pp. 64, lines 24-26. Specific support for hOP-1 is found on pg. 65, lines 16-19. Appropriate hybridization conditions (*i.e.*, temperature, duration, hybridization mix, washes) are provided at specification page 66, lines 4-10. Although these teachings are directed to the determination of tissue distribution, the specification indicates that the probes and hybridization methods can be used to "identify new, related morphogens" and for "screening and identifying candidate morphogen-stimulating agents" (*see*, specification page 64, lines 8-12).

Applicants have canceled claims 86-87 and inserted new claims 105-106 to eliminate dependency on canceled claims. No new matter is added by the present amendments.

PROVISIONAL SAME INVENTION DOUBLE PATENTING REJECTION

The Examiner has provisionally rejected claims 94-104 under 35 U.S.C. § 101 as claiming the same invention as that of claims 13-23 of co-pending patent application 08/937,755. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. Applicants respectfully request that the rejections be held in abeyance pending a determination of otherwise allowable claims in the present application.

PROVISIONAL OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

The Examiner has rejected provisionally claims 82-93 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of co-pending patent application 08/937,755. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Applicants respectfully request that the rejections be held in abeyance pending a determination of otherwise allowable claims in the present application.

§ 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION, REJECTIONS

The Examiner has rejected claims 82, 84-88, 90-91, 93, and 103-104 under 35 U.S.C. § 112, first paragraph, written description. The Examiner alleges that "no conception nor proper antecedent basis is apparent for a sequence having "at least 70% / greater than 60%... from the C-terminal seven-cysteine skeleton... residues 38-1 39" (*i.e.*, versus "the amino acid sequence defining the conserved six cysteine skeleton of hOP-1 (*e.g.*, residues 43-139 of SEQ ID NO. 5)", as disclosed on page 53 of the specification (*i.e.*, as it relates to claims 82, 84, 88, 90-91 & 93)" (*see,* Office action, pg. 4). Applicants traverse.

This rejection is "without observance of procedure required by law" Administrative Procedures Act, 5 U.S.C. § 706(2)(D). The *Manual of Patent Examining Procedure (MPEP),* 7th Edition, § 2163 The Written Description Requirement, states that:

> An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed.
>
> Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed. The subject matter of the claim need not be described literally (*i.e.*, using the same terms or in *haec verba*) in order for the disclosure to satisfy the description requirement.

MPEP § 2163.02. Moreover,

> The examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. 541 F.2d at 265, 191 USPQ at 98. See also *Ex parte Sorenson*, 3 USPQ2d 1462, 1463 (Bd. Pat. App. & Inter. 1987).

MPEP § 2163.04. Conception for the recited morphogen structure is demonstrated by the abundant detail provided in the specification. Support for the recitation of morphogen structure having a sequence having at least 70% amino acid homology with the C-terminal seven-cysteine domain of human OP-1, amino acids 38-139 of SEQ ID NO:5 is found in the specification, pg. 39, line 33, to pg. 40, line 1 (describing sequences "sharing 70% amino acid sequence homology . . . with any of the sequences listed above" including those sequences in Table I); pg. 46, lines 6-12; pg. 53, lines 11-25 (*citing*, Dayoff *et al.*, 5(3) *Atlas of Protein Sequence and Structure* 345-362 (Dayoff, ed., Natl. Biomed. Res. Found., 1979)) for then-state of the art methods for determining homology). Support for the recitation of morphogen structure having a sequence having greater than 60% amino acid sequence identity with said C-terminal seven-cysteine domain of human OP-1 is found in the specification, pg. 40, lines 20-34; and on pg. 53, lines 26-35. Support for the recitation of morphogen structure having a sequence defined by Generic Sequence 6, SEQ ID NO:31 is found in the specification, pg. 33 , line 16, to pg. 39, line 18. Support for the morphogen stimulating production of an N-CAM or L1 isoform by an NG108-15 cell *in vitro* is found in the specification, pg. 76, line 1, to pg. 80, line 17, Example 6.

In summary, the specification adequately describes, in legally sufficient detail, the recited morphogen structure.

The Examiner alleges that there is no conception for the recitation, "complexed with at least one morphogen pro domain polypeptide." Applicants disagree, because adequate written description for a morphogen complexed with a morphogen pro domain polypeptide is clearly provided in the specification, *for example*, on pg. 18. Applicants also disagree that the recitation of multiple or different polypeptide pro domains to the recited morphogens legally constitutes new matter.

However, to advance prosecution, Applicants have canceled claims 103 and 104 without prejudice. This rejection is thus moot and should be withdrawn.

The Examiner alleges that no conception nor antecedent basis appears in context of that disclosed within the specification for "treating", "restoring motor function", or "preserving motor function" in a mammal afflicted with ALS or spinal cord injury. Applicants disagree, and also disagree that the introduction of these claims by amendment constitute new matter. The original claims 10 and 39 were directed to a method "for enhancing survival of neural cells at risk of dying" or "maintaining a neural pathway" and amending a claim does not add new matter to the disclosure. "Disclosure is that which is taught, not that which is claimed. An applicant is entitled to claims as broad as the prior art and his disclosure will allow." *In re Rasmussen*, 211 USPQ 323, 326 (CCPA 1981).

To advance prosecution, Applicants have canceled claims 82, 84, 93-94, 96, 100, and 102 without prejudice. Regarding the claims to restoration of motor function, the specification provides adequate guidance for the administration of morphogen (*see, for example,* specification, pp. 54-63). The specification also teaches that administration of morphogen results in restoration of functional neural pathway (*see,* specification, pg. 8, lines 9-16).

Accordingly, Applicants respectfully request that these rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

§ 112, FIRST PARAGRAPH, ENABLEMENT, REJECTIONS

The Examiner has rejected claims 82, 84-88, 90-9 1, 93-94, 96-97, 99-100 and 102-104 under 35 U.S.C. § 112, first paragraph. The Examiner alleges that the specification enables a method of using OP-1 of SEQ ID NO:4 or 5 to induce N-CAM and L1 expression in NG-108 cells. However the Examiner alleges that the specification does not enable restoring motor function in a mammal with ALS or spinal cord injury, or for using structurally uncharacterized morphogens or biologically functional equivalents thereof to accomplish such. Applicants traverse.

As an initial matter, the claims do not recite a method of inducing N-CAM expression in NG108 cells. The stimulation of N-CAM or L1 isoform production by an NG108-15 cell *in vitro* is a functional limitation on the morphogen, not a step in the claimed methods.

Furthermore, in making the determination of enablement, the examiner shall consider the original disclosure and all evidence in the record, weighing evidence that supports enablement against evidence that the specification is not enabling. MPEP § 2164.05. Applicants respectfully ask the Examiner to reconsider the pending enablement rejection. Applicants submit that the Examiner has not adequately weighed the evidence of the specification and prior art that supports enablement. *First*, the Examiner misreads the specification regarding the working examples provided in the specification. *Second*, the Examiner misreads the specification regarding the state of the art at the time of filing. *Third*, the Examiner misreads the state of the art.

The Examiner misreads the specification regarding the working examples provided in the specification.

The Examiner alleges that several of the working examples in the specification do not show morphogen effectiveness. In doing so, the Examiner has drawn several interpretations from the working examples that contest the teaching of the specification. Applicants reply that "without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). In situations in which two interpretations of statements in a specification are possible and

feasible, Applicant's interpretation should be fully considered and can be accepted. *In re Soni*, 54 F.3d. 746, 34 USPQ 1684 (Fed. Cir. 1995).

The specification provides a working example of neural regeneration on pg. 80-82, Example 7, in which a 12 mm gap is traversed in a rat sciatic nerve graft experiment using a silicone tube filled with OP-1 (morphogen) gel. The Examiner alleges that "one graft site containing *no* OP-1 also showed axonal growth of 12 mm." (*see,* Office action, pg. 5). That is not what the specification teaches:

> Regeneration of the sciatic nerve occurred across the entire 12 mm distance in all graft sites wherein the gap was filled with the OP-1 gel. By contrast, empty silicon tubes and reverse autographs did not show nerve regeneration, and only one graft site containing the gel alone showed axon regeneration.

(*see,* specification, pg. 82, lines 23-28). From this incorrect premise, the Examiner makes an incorrect conclusion, that "axonal growth for 12 mm is not dependent on OP-1". Applicants reply that the Examiner's allegation is statistically unfeasible.

In summary, the Examiner has not shown why the Applicants interpretations of the specification are not correct. Accordingly, Applicants respectfully request that the working examples provided in the specification be reconsidered and accepted as evidence for enablement. The specification clearly supports Applicant's interpretation as a fair reading of this statement. By contrast, the Examiner has given no specific reasons which can be addressed. Accordingly, Applicants request that this position no longer be maintained by the Examiner, and the issue be considered resolved.

The Examiner misreads the specification regarding the state of the art at the time of filing.

The Examiner alleges that the specification, pg. 3, summarizes the state of the art in which "[c]urrently, no satisfactory method exists to repair the damage caused by these neuropathies, which include multiple sclerosis, amyotrophic lateral sclerosis (ALS)." This allegation is incorrect.

The quoted statement is found in the BACKGROUND, describes the state of the art ***before*** the invention described in the application, and so does not accurately describe the state of the art at the time of the filing.

The Examiner misreads the state of the art in making the enablement rejection.

(1) The Examiner cites Lein *et al.*, 15(3) Neuron 597-605 (1995) ("*Lein*") and then alleges that "without NGF there is no neurite outgrowth/synaptic contact/motor function. Without OP-1 there is still outgrowth in culture. Therefore, OP-1 is inert" (*see,* Office action, pg. 6). This allegation is incorrect.

Lein does ***not*** allege that morphogen is inert, quite the contrary. The title of *Lein* is "*Osteogenic Protein-1 Induces Dendritic Growth in rat Sympathetic Neurons.*" The content of *Lein* demonstrates that morphogen is ***active*** in inducing neurites. Thus, *Lein* supports, rather than contradicts, the specification regarding the effectiveness of morphogen administration. For both *Lein* and the specification, morphogen is ***not*** inert.

(2) The Examiner cites Varley *et al.*, 203 Developmental Dynamics 434-447 (1995) ("*Varley*"), then alleges that "because neurons, by definition, are postmitotic/amitotic after birth, this reference clearly establishes that the instant invention can not work *in vivo* in a mammal without undue experimentation to determine otherwise" (*see,* Office action, pg. 6). This allegation is incorrect.

The Examiner misreads *Varley*. When *Varley* states that "OP-1 does not act on a postmitotic cell population" (*Varley,* pp. 441-442), *Varley* is measuring "increase in adrenergic cell number" (*Varley,* pg. 441) and not dendrite outgrowth or synaptic formation. The pending claims are not directed to increasing adrenergic cell number. Thus, *Varley,* pp. 441-442, is irrelevant to the pending claims.

(3) The Examiner alleges that Wilson *et al.*, 376(6538): Nature 331-3 (1995) ("*Wilson*") disclose that bone morphogenetic proteins (BMPs) do not predictably enhance synaptic contacts/motor function, in that BMP-4 is a "neural inhibitor" (*citing* Wilson, pg. 331, Abstract). This allegation is incorrect.

Wilson is profoundly irrelevant to the claimed methods. *Wilson* investigates "gastrulation in vertebrates", a developmental time period during which "ectodermal cells choose between two fates, neural and epidermal." During this developmental time period, there is no nervous system, hence no neurons, hence no neurites, hence no synapses. During this developmental time period, "bone morphogenesis protein 4 (Bmp-4), a relative of activin that is expressed in the embryo at the time of ectodermal fate determination, is a potent epidermal inducer and neural inhibitor" of

the developmental switch, not of dendrite formation or synaptogenesis. This event has nothing to do with the claimed methods. In summary, *Wilson* is irrelevant to the pending claims.

(4) The Examiner cites Withers *et al.*, Soc. Neurosci. Abstr. (1996) ("*Withers*") and alleges that "Withers et al. appear to establish that the claimed invention does not work *in vitro*." (*see,* Office action, pg. 6). This allegation is incorrect.

The Examiner quotes the middle portion of *Withers,* that "no synaptic contacts were observed", which result raises "two possibilities: 1) the OP-1 induced dendrites were not receptive to innervation; or 2) the poor growth of axons in these cultures prevented normal synaptic contacts from occurring" (*see,* Office action, pg. 7).

However, the Examiner does not quote and selectively ignores the ***beginning*** and the ***end*** of *Withers. Withers* begins with the statement that: "Previously, we reported that OP-1 . . . induced dendritic development in hippocampal cultured neurons." Later, after discussing the previously reported lack of synaptic contact (quoted above), *Withers* then reports that "we found evidence of synapsin positive aggregates, surrounding OP-1 induced neurites, indicative of early stages of synapse formation. In summary (and in contradiction to the interpretation provided by the Examiner), *Withers* reports positive results regarding the ability of OP-1 to induce dendrites on neurons, dendrites that are capable of forming synapses *in vitro,* and by analogy *in vivo.*

(5) The Examiner alleges that the state of the art is that no regeneration occurs in the central nervous system. This allegation is incorrect as a matter of scientific fact; regeneration is now well-known in the art to occur in mammals, in humans.

The Examiner alleges that Jackowski, British J. Neurosurg. 303-317 (1995) ("*Jackowski*") teaches that CNS neurons do not regenerate. However, the Examiner's interpretation of *Jackowski* does ***not*** represent the state of the art as of the filing date. *Jackowski* does not state, nor was it the state of the art at the time of the filing, that nerve regeneration does not occur in mammals. Indeed, the evidence presented by *Jackowski* shows that nerve regeneration, even nerve regeneration in the CNS, ***had already been shown*** (*see, Jackowski,* ref. 135-139, citing the work of Schwab, and ref. 140-141, citing the work of Schachner). What has already been shown cannot be considered to be impossible. Therefore, under the appropriate circumstances, such as those disclosed in the specification, nerve regeneration can occur.

(6) The Examiner alleges that dead neurons characterize ALS and spinal cord injury. This is scientifically and legally irrelevant to the pending claims.

First, the fact that dead neurons characterize these diseases does not gainsay the fact that ***living*** neurons ***also*** characterize these diseases. Clearly, a person whose central nervous system contains only dead cells is not suffering from a disease; that person is dead. *Second*, neither the specification nor any reference teaches that neuronal contacts are permanently lost and cannot be restored. The connection in these diseases is lost because the target cell deteriorates. Connections are formed on other target cells. *Third*, none of the claims involve making connections on dead cells. Therefore, there is no legal requirement for the specification to enable making connections on dead cells. In summary, the issue of connections on dead cells is irrelevant to the enablement of the pending claims.

(7) The Examiner alleges that the NG108-15 is not representative of any *in vivo* nervous system tissue. While Applicants disagree with the Examiner as to whether NG108-15 is a neurobiological art-accepted model, the disagreement is nevertheless moot.

Applicants have amended the claims to introduce subheadings, to show that the stimulation of N-CAM or L1 isoform production by an NG108-15 cell *in vitro* is a functional limitation on the morphogen, not a step in the claimed methods.

(8) The Examiner alleges that the only nexus between the results of the specification and treatment of ALS or spinal cord injury, is that in all these instances, the neuronal populations eventually die; thereby, preventing formation of synaptic contacts. Applicants disagree.

The "stimulation of N-CAM or L1 production " is ***not*** the nexus. The nexus is the formation of connections between neurons, to restore motor function. Thus, the claims are commensurate in scope with that disclosed within the specification for treating ALS or spinal cord injury.

(9) The Examiner alleges "it is well accepted in the art the differences exist between *in vitro* protocols and results, versus *in vivo* protocols and results, especially as it relates to undefined parameters that do not distinguish when "treatment" is effective, or that involve undefined parameters that do not distinguish "treatment" of "ALS", for example, from any different disease state. Applicants demur, because the Examiner does not use the correct legal standard.

"If reasonably correlated to the particular therapeutic or pharmacologic utility, data generated using *in vitro* assays, or from testing in an animal model or combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition, or process." MPEP § 2107. The enablement analysis should be based on whether there is evidence that one skilled in the art could ***not*** have used the compound for the restoration of motor function, as recited in the claims as amended.

The specification as filed teaches that administration of morphogen results in restoration of functional neural pathway (*see,* specification, pg. 8, lines 9-16). At a later time, Applicants will provide further declaratory evidence that such administration results in restoration of motor function.

Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

The Examiner has rejected claims 94, 96-97, 99-100 & 102-104 for lack of enablement. The Examiner alleges that the name "morphogen" as it relates to the generic sequences sets forth little or no structural characteristics, and little functional characterization. The Examiner alleges that the "specification does not teach which specific amino acids are critical for any morphogen function, nor how to distinguish such from any different polypeptide sequences that possess none of the desired functions of the instant invention., yet are encompassed by the claims" (*see,* Office action, pg. 7). Applicants respectfully traverse.

The Examiner cites Rudinger, in *Peptide Hormones*, Parsons, ed., pg. 3 (University Park Press, Baltimore, 1976) that "it is impossible to attach a unique significance to any residue in a sequence. A given amino acid will not by any means have the same significance in different peptide sequences, or even in different positions of the same sequence". However, the disclosure of Rudinger are not directly applicable to the pending claims.

First, Rudinger concerns the prediction of peptide activity based upon purely structural consideration. By contrast, the pending claims recite both structural and functional considerations. *Second, Rudinger* does not represent the state of the art at the date of filing. The 1976 disclosure of *Rudinger* had been supplanted before the date of filing (a) by the 1979 disclosure of Dayoff *et al.*, 5(3) *Atlas of Protein Sequence and Structure* 345-362 (Dayoff, ed.,

Natl. Biomed. Res. Found., 1979) ("*Dayoff*")) (*see,* specification, pg. 18) and later investigators; (b) by the guidance of the specification regarding morphogen structural and functional characteristics; and (c) the assays of Examples 3, 10, and 11), that eliminate the need for "painstaking experimental study" (*Rudinger*, pg. 6).

Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

§ 112, SECOND PARAGRAPH, REJECTIONS

The Examiner has rejected claims 82, 84-88, 90-91, 93-94, 96-97, 99-100, and 102-104 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants traverse.

The Examiner alleges that it is ambiguous why the physically and functionally distinct "N-CAM or L1 isoform" production by "NG108-15 cells *in vitro*" would be any indication for "treating/preserving motor function/restoring motor function" in a mammal afflicted with ALS or spinal cord injury, as currently recited. This is not a proper indefiniteness rejection. As written, the production of N-CAM or L1 isoforms by NG108 cells is a ***functional*** limitation on the ***morphogen***, not a result of the practice of the method. The production of N-CAM or L1 isoforms by NG108 cells provides a routine, simple assay permitting a skilled artisan to distinguish a morphogen from structurally-related non-morphogens.

The Examiner also alleges that the methods are incomplete for omitting essential steps, in which such omissions amount to a gap between the steps. Applicants disagree. There are no gaps between the steps. There is only one step - administer the morphogen. Administering the morphogen constitutes the treating, preserving or restoring motor function recited in the preambles. However, to advance prosecution, Applicants have amended the claims to recite the restoration of motor function. This rejection is thus moot and should be withdrawn.

The Examiner has rejected claims 94, 96-97, 99-100 and 102-104 as being indefinite because CBMP2 (in the specification, pg. 23) "appears to indicate that CBMP2 is equivalent to BMP2A and/or BMP2B, thereby, reciting duplicative members of the Markush group." The Examiner is incorrect; the claims do not recite duplicative members. The specification, pg. 23, shows that BMP2A and BMP2B have different polypeptide sequences (*see,* lines 12-17, the two

proteins have different lengths, different pro domains, and are different mature proteins). BMP2A and BMP2B are thus patentably distinct.

Accordingly, Applicants request that this rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

The Examiner has rejected claims 82, 84-88, 90-91, 93, and 103-104, as being indefinite because the recitation of a "% identity/homology" is indefinite. The Examiner alleges that it is not known what is envisioned to meet this limitation, since the algorithm used to calculate the percent identity, or those parameters (*e.g.*, gap penalties, mismatch penalties) required to determine such, are not disclosed within the specification. Applicants traverse.

The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). "If the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, (35 U.S.C. § 112, second paragraph) demands no more." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81 (Fed. Cir. 1986). Here, the claims read in light of the specification (*see especially,* pp. 17-29), make clear the utilization and scope of the recited morphogens.

The Examiner is mistaken regarding whether the algorithm used to calculate the percent identity, or those parameters (*e.g.*, gap penalties, mismatch penalties) required to determine such, are disclosed within the specification. The specification shows that the Applicants had arranged the amino acid sequences of morphogens known at the filing of the application to identify the conserved portions of the peptide (*see,* specification, pg. 46, line 23, to pg. 53, line 15, *including* Table II). Applicants also defined the terms "homology" (specification, pg. 39, line 33, to pg. 40, line 18; and pg. 53, lines 18-25, *both citing,* Dayoff *et al.*, 5(3) *Atlas of Protein Sequence and Structure* 345-362 (Dayoff, ed., Natl. Biomed. Res. Found., 1979)) and "identity" (having the commonly understood meaning, *see,* specification, pg. 53, lines 15-18). Applicants then calculated the % homology and the % identity for the morphogens. The specification cites to a reference that provides algorithms for aligning sequences (specification, pg. 40, lines 11-18; and on pg. 46, line 34, to pg. 47, line 2, *both citing*, Needleman *et al.*, 48 J. Mol. Biol. 443-53

(1970)). Furthermore, the specification teaches how to treat gaps in the amino acid sequences of the morphogens (*see,* specification, 47, lines 5-8).

In summary, the specification clearly apprises those skilled in the art how to scientifically determine whether or not a peptide is a morphogen as recited in the claims. Accordingly, Applicants request that this rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

The Examiner has rejected claims 103-104, because they are dependent on non-elected base claims. Applicants have canceled claims 103 and 104. This rejection is thus moot and should be withdrawn.

THE § 102 REJECTION

The Examiner has rejected claims 82, 84-88, 90-91, 93 & 103-104 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by PCT International patent application WO 95/06656 ("*Harland*"). The Examiner has also accorded the present application a priority date of September 25, 1997. Applicants traverse this rejection and submit that both the rejection and the accorded filing date are logically inconsistent and unfair.

The first parent application of the present application is United States patent applications 08/292,782, filed August 18, 1994, with a priority date through file wrapper continuations of July 31, 1992. The present application is a continuation-in-part of the '782 application. The second parent application is 08/260, 675, filed June 16, 1994. The present application is a continuation of the '675 application. The Examiner alleges that the parent applications are not enabling for the present application. Applicants disagree.

To make an rejection, the examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure [of the parent applications]. MPEP § 2164.04. However, the Examiner has presented ***no*** reasons for showing ***why*** the parent applications do not enable the claimed methods. The Examiner merely makes an unsupported allegation that the parent applications are not enabling for the treatment of ALS and other conditions characterized by necrosis or loss of neurons.

Moreover, the Examiner has presented no reasons for showing why *Harland* ***does*** enable the claimed methods. For a publication to constitute an anticipation of an invention, the "prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of

the public." *Akzo N.V. v. U.S. International Trade Commission*, 1 USPQ 2d 1241, 1245 (Fed. Cir. 1986), *cert. denied*, 482 U.S. 909 (1987); *In re Donohue*, 632 F.2d 123, 207 USPQ 196 (CCPA 1980); *Ex parte Humphreys*, 24 USPQ 2d 1255, 1261-62 (BPAI 1992). The Examiner alleges that *Harland* disclose a "method of enhancing survival of nerve cells in a mammal, and treatment of ALS (i.e., restoring/preserving motor function) and "other conditions characterized by necrosis or loss of neurons, whether central, peripheral or motor neurons" (*i.e.*, including the motor neurons affected during spinal cord injury), and "nerves damaged by traumatic conditions..., and the toxic effects of chemotherapeutics" (*i.e.*, including mechanical/tumor-induced and chemical injury; as it relates to claims 85-87) through administering the morphogen, dor3 (*citing, Harland*, pp. 13-14). A review of *Harland* shows that the description cited by the Examiner is ***one paragraph*** of general description.

Contrast the limited disclosures of *Harland* with the teachings of the first parent application 08/292,782, which provides guidance for the administration of morphogen in methods for stimulating dendrite outgrowth (*see,* specification, pg. 11, line 21, to pg. 12, line 2; on pg. 14, lines 5-12; on pg. 25, line 33, to pg. 26, line 32; and on pp. 114-122, Examples 13-16), methods of preserving integrity of a neural pathway (*see,* specification, pg. 12, lines 3-26), and methods for stimulating repair of a damaged mammalian neural pathway (*see,* specification, pg. 14, lines 13-31; on pg. 27, lines 1-8; pp. 101-103, Example 7). The concept of alleviating neurodegenerative diseases is found in the specification (*see,* specification, pg. 10, lines 3-14; and on pg. 27, lines 17-30). Conception for morphogen structure is found on pp. 9-12, 24, and 114-124; and 5-6, 16-17, 19-20, 27-28, 37, 49, and 51. Support for the recited structure of the morphogens is especially found in the specification on pg. 29, line 5, to pg. 48, line 20, including Table I; and on pg. 58, line 26, to pg. 66, line 4, including Table II. The specification provides guidance for administering the morphogens (*see,* specification, pg. 66, line 5, to pg. 76, line 30). The specification also provides several working examples of the claimed methods.

Contrast also the limited disclosures of *Harland* with the teachings of second parent application 08/260,675 (and the present application), which provides for the recitation of morphogen structure having a sequence having at least 70% amino acid homology with the C-terminal seven-cysteine domain of human OP-1 is found in the specification, pg. 39, line 33, to pg. 40, line 1 (describing sequences "sharing 70% amino acid sequence homology . . . with any

of the sequences listed above" including those sequences in Table I); pg. 46, lines 6-12; pg. 53, lines 11-25 (*citing*, Dayoff *et al.*, 5(3) *Atlas of Protein Sequence and Structure* 345-362 (Dayoff, ed., Natl. Biomed. Res. Found., 1979)) for then-state of the art methods for determining homology). Support for the recitation of morphogen structure having a sequence having greater than 60% amino acid sequence identity with said C-terminal seven-cysteine skeleton of human OP-1 is found in the specification, pg. 40, lines 20-34; and on pg. 53, lines 26-35. A method for repairing a damaged neural tissue is found in the specification, pg. 8, lines 9-17. The specification provides a working example of morphogen-induced repair of a neural pathway on pg. 80, line 20, to pg. 82, line 28, Example 7.

The Examiner cites *In re Ahlbrecht*, 435 F.2d 908, 168 USPQ 293 (CCPA 1971). A review of *Ahlbrecht* shows that in that case, the disclosure of parent application may well have enabled production of claimed esters (*Ahlbrecht*, 168 USPQ at 296). That situation is similar to the relationship between the present application and its parent applications, where the parent applications teach how to make and administer the morphogens of the present application to achieve neurological results. But in *Ahlbrecht,* the disclosure of parent application only described esters, thus failing the written description requirement. By contrast, the continuing record of prosecution shows abundant written description in both the parent applications (*see, above*), a written description that continues into the present application.

It is ***logically inconsistent*** to conclude that the limited disclosure of *Harland* provides sufficient written description or enablement to anticipate the pending claims, while concluding that the abundant disclosure of the first parent application and second parent application (and thus the present application) does not provide sufficient enablement for a claim of priority. It is also ***unfair*** to the Applicants to be held to an apparently different legal standard than is applied to *Harland.*

Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 102(b) be withdrawn.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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